

**REMARKS**

Claims 1-4, 7, 8, 14, 15, 22-24, and 37-38 are pending in this application. Claims 5, 6, 9-13, 16-21, 25-36, and 39-60 have been cancelled previously. Claims 61-76 have been cancelled as being directed to a non-elected invention.

**Rejection under 35 U.S.C. §103**

Claims 1-4, 7, 8, 14, 15, 22-24, 27, 37, 38 and 61-76 have been rejected under 35 U.S.C. §103(a) as obvious over Pettit *et al.*, WO99/35150 (“Pettit”), in view of Cahan *et al.*, Cancer Chemotherapy and Pharmacology, 33(5):441-4 (1994) (“Cahan”). Applicants traverse for the reasons discussed below.

According to the Examiner, Pettit teaches the compound, Combretastatin A4 Phosphate (“CA4P”), for the treatment of one or more neoplastic diseases, such as malignant melanoma, breast carcinoma, and ovarian carcinoma in humans. The Examiner also states that Cahan teaches that taxol has shown clinical activity against several tumors, including ovarian and breast carcinoma and melanoma. The Examiner concedes that Pettit and Cahan do not teach the combination together. However, the Examiner argues that “one skilled in this art would find ample motivation from the prior art supra to combine the well know [sic] anticancer agents together where the results obtained thereby are no more than the additive effects of the anticancer agents; particularly since the above prior art teaches the ingredient for treating the same cancer systems.” Office Action dated 06/01/2004 at page 3.

Applicants submit that it would not have been obvious to one of ordinary skill in the art to have used CA4P and its analogs in combination with taxanes and its analogs as the combination as recited in the pending claims has demonstrated highly unexpected results. Submitted with this response is a Declaration by a skilled artisan describing such highly unexpected results.

The attached Declaration by Dr. Sally Hill, a Senior Scientist in the Tumor Microcirculation Group at the Gray Cancer Institute in London , United Kingdom, describes a synergistic effect on tumor cell survival by combining CA4P and taxol. The synergistic property of the combination therapy was unexpected in view of the biological mechanisms attributed to each agent. Taxol binds to polymerized microtubules, thereby inhibiting their depolymerization and arresting tumor cell

division. Whereas, CA4P binds to  $\beta$ -tubulin monomers and prevents their assembly into microtubules. Therefore, one of skill in the art of anti-cancer therapy at the time of the invention would have expected CA4P to antagonize the effects of taxol and vice versa. Thus, Applicants assert that one skilled in the art would not have found motivation from the prior art to combine these anti-cancer agents.

Moreover, the anti-tumor results obtained are more than additive effects of the individual agents. In experiments performed in Dr. Hill's laboratory, mice bearing a murine adenocarcinoma NT (CaNT) tumor were treated with CA4P (50 mg/ml), taxol (30 mg/ml), both (CA4P (50 mg/ml) + taxol (30 mg/ml)) or saline. The results in terms of percent tumor cell kill were: 87% for CA4P alone, 64% for taxol alone, and 97.7% for CA4P + taxol. Expressed as mean tumor cell survival fraction per gram of tumor ("S.F./g), the corresponding values are 0.134 for CA4P alone, 0.3574 for taxol alone, and 0.0233 for CA4P + taxol. Based on the anti-tumor effects observed for each individual agent, an additive effect would have provided a surviving fraction of 0.048 or a 95.2% reduction in tumor cell viability. Furthermore, the amount of cell kill observed with the CA4P + taxol combination is over a factor of two greater than the amount of cell kill obtained with CA4P alone. Therefore, it was concluded that the results were not merely an additive effect of the combination, but a greater than additive *i.e.*, synergistic effect.

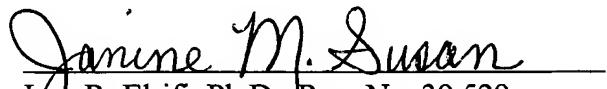
In view of the superior and surprising properties of the CA4P + taxol combination therapy as described in the accompanying Declaration, Applicants submit that one of ordinary skill in the art would not find the methods recited in the pending claims to be obvious over the combined teachings of Pettit and Cahan.

**CONCLUSION**

In view of the aforementioned remarks and amendments, the Applicants believe that each of pending claims is in condition for allowance. Reconsideration, withdrawal of the rejections, and passage of the case to issue is respectfully requested. A notice to this effect is earnestly solicited.

If, upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicant's undersigned counsel at the number provided below.

Respectfully submitted,

  
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